

10/538452

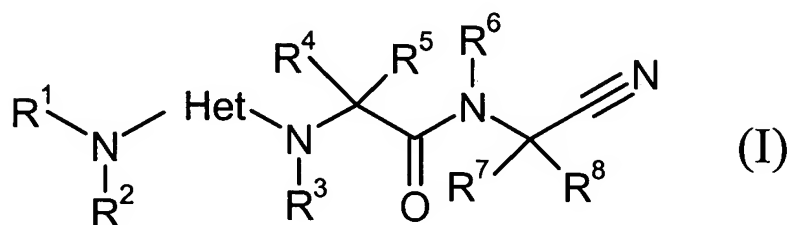
JC17 Rec'd PCT/PTO 10 JUN 2005

Amendments to the Claims:

This listing of claims replaces all prior versions and listings of claims in the application.

Listing of Claims:

1. (Currently amended) A compound of formula (I):



R¹ is independently hydrogen, C₁₋₆ alkyl or C₃₋₆ cycloalkyl;

R² is independently aryl, heteroaryl or a group C₁₋₆ alkylR⁹, CO(C₁₋₆ alkyl)R⁹ or SO₂(C₁₋₆alkyl)R⁹; where R⁹ is aryl or heteroaryl;

or R¹ and R² together with the nitrogen atom to which they are attached form a 4 to 7-membered saturated ring optionally containing a carbonyl group, O, S or N atom and optionally substituted by one or more C₁₋₆ alkyl, amino, hydroxy, CO₂C₁₋₆ alkyl, COC₁₋₆ alkyl, halogen, C₁₋₆ alkylhydroxy, NR¹⁰R¹¹ where R¹⁰ and R¹¹ are independently hydrogen, C₁₋₆ alkyl or together with the nitrogen atom to which they are attached form a 5- or 6-membered saturated ring optionally containing a further O, S or NR¹ group, C₁₋₆ alkylNR¹²R¹³ where R¹² and R¹³ are independently hydrogen or C₁₋₆ alkyl, CONR¹²R¹³, or optionally substituted by C₁₋₆ alkylR⁹, aryl, phenoxy, COaryl, COheteroaryl or a heteroaryl group, the latter six groups being optionally substituted by halogen, amino, hydroxy, cyano, nitro, carboxy, CONR¹²R¹³, SO₂NR¹²R¹³, SO₂R¹², trifluoromethyl, NHSO₂R¹², NHCOR¹², ethylenedioxy, methylenedioxy, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkyl NR¹⁰R¹¹, SR¹² or NR¹⁰R¹¹;

Het is a heteroaryl ring chosen from pyridine, pyrimidine, pyrazine, pyridazine or triazine and optionally substituted by halogen, amino, hydroxy, cyano, nitro, carboxy, $\text{CONR}^{12}\text{R}^{13}$, $\text{SO}_2\text{NR}^{12}\text{R}^{13}$, SO_2R^{12} , trifluoromethyl, $\text{NHSO}_2\text{R}^{12}$, NHCOR^{12} , C_{1-6} alkyl, C_{1-6} alkoxy, SR^{12} or $\text{NR}^{10}\text{R}^{11}$;

R^3 is independently hydrogen, C_{1-6} alkyl or C_{3-6} cycloalkyl;

R^4 is independently hydrogen, C_{1-8} alkyl, C_{3-8} cycloalkyl, aryl C_{1-5} alkyl or heteroaryl C_{1-5} alkyl, the latter three groups being optionally substituted by one or more halogen, amino, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, SR^{12} or $\text{NR}^{10}\text{R}^{11}$;

R^5 is independently hydrogen, C_{1-6} alkyl or C_{3-6} cycloalkyl;

R^6 is independently hydrogen, C_{1-6} alkyl or C_{3-6} cycloalkyl;

R^7 is independently hydrogen, C_{1-6} alkyl or C_{3-6} cycloalkyl; and

R^8 is independently hydrogen, aryl, heteroaryl or C_{1-6} alkyl optionally substituted with one or more aryl, heteroaryl, halogen, amino, hydroxy, carboxy, $\text{CONR}^{12}\text{R}^{13}$, $\text{SO}_2\text{NR}^{12}\text{R}^{13}$, SO_2R^{12} , $\text{NHSO}_2\text{R}^{12}$, NHCOR^{12} , C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, SR^{12} or $\text{NR}^{10}\text{R}^{11}$;
or a pharmaceutically acceptable salt thereof.

2. (Original) A compound according to claim 1 in which R^1 is hydrogen or C_{1-6} alkyl and R^2 is CH_2R^9 or $\text{CH}_2\text{CH}_2\text{R}^9$ where R^9 is phenyl or a 5- or 6-membered aromatic ring containing one or two heteroatoms and optionally substituted by C_{1-6} alkyl.

3. (Currently amended) A compound according to claim 1 ~~[[or 2]]~~ in which R^1 and R^2 together with the nitrogen atom to which they are attached form a piperidine, piperazine, pyrrolidine, morpholine, or thiomorpholine ring optionally substituted by CH_2OH , $\text{CH}_2\text{CH}_2\text{OH}$, hydroxy, CONH_2 , phenyl, phenoxy, or $\text{C}(\text{O})$ -furyl, the latter three groups being optionally substituted by halogen, in particular chloro.

4. (Currently amended) A compound according to ~~any one of claims 1 to 3~~ claim 1 in which R^3 is hydrogen.

5. (Currently amended) A compound according to ~~any one of claims 1 to 4~~ claim 1 in which R⁴ is hydrogen.

6. (Currently amended) A compound according to ~~any one of claims 1 to 5~~ claim 1 in which R⁵ is hydrogen or phenyl optionally substituted by C₁₋₆ alkyl or C₁₋₆ alkoxy.

7. (Currently amended) A compound of formula (I) selected from:

N~1~[Cyano(2-methoxyphenyl)methyl]-N~2~(2-morpholin-4-ylpyrimidin-4-yl)-L-leucinamide₂

N~1~[Cyano(2-methoxyphenyl)methyl]-N~2~(2-piperazin-1-ylpyrimidin-4-yl)-L-leucinamide₂

N-[Cyano(2-methoxyphenyl)methyl]-N-(2-morpholin-4-ylpyrimidin-4-yl)-L-phenylalaninamide₂

N~1~[Cyano(2-methoxyphenyl)methyl]-3-cyclohexyl-N~2~(2-morpholin-4-ylpyrimidin-4-yl)-L-alaninamide₂

N-[2-(Benzylamino)pyrimidin-4-yl]-N-(cyanomethyl)-L-phenylalaninamide₂

N-{2-[Benzyl(methyl)amino]pyrimidin-4-yl}-N-(cyanomethyl)-L-phenylalaninamide

N-{2-[4-(4-Chlorophenyl)piperazin-1-yl]pyrimidin-4-yl}-N-(cyanomethyl)-L-phenylalaninamide₂

N~2~[2-(Benzylamino)pyrimidin-4-yl]-N~1~(cyanomethyl)-3-cyclohexyl-L-alaninamide₂

N~2~{2-[Benzyl(methyl)amino]pyrimidin-4-yl}-N~1~(cyanomethyl)-3-cyclohexyl-L-alaninamide₂

N~2~{2-[4-(4-Chlorophenyl)piperazin-1-yl]pyrimidin-4-yl}-N~1~(cyanomethyl)-3-cyclohexyl-L-alaninamide₂

N~1~(Cyanomethyl)-N~2~(4-morpholin-4-ylpyrimidin-2-yl)-L-leucinamide₂

N~1~(Cyanomethyl)-N~2~(2-morpholin-4-ylpyrimidin-4-yl)-L-leucinamide₂

N~1~-(Cyanomethyl)-N~2~-{2-(4-hydroxy-4-phenylpiperidin-1-yl)pyrimidin-4-yl}-L-leucinamide,₁

N~1~-(Cyanomethyl)-N~2~-{2-[methyl(pyridin-3-ylmethyl)amino]pyrimidin-4-yl}-L-leucinamide,₁

N~2~-{2-[Benzyl(methyl)amino]pyrimidin-4-yl}-N~1~-(cyanomethyl)-L-leucinamide,₁

N~2~-{2-[4-(4-Chlorophenyl)piperazin-1-yl]pyrimidin-4-yl}-N~1~-(cyanomethyl)-L-leucinamide,₁

N~2~-{2-[4-(5-Chloropyridin-2-yl)piperazin-1-yl]pyrimidin-4-yl}-N~1~-(cyanomethyl)-L-leucinamide,₁

N~1~-(Cyanomethyl)-N~2~-{2-[methyl(thien-3-ylmethyl)amino]pyrimidin-4-yl}-L-leucinamide,₁

N~1~-(Cyanomethyl)-N~2~-(2-thiomorpholin-4-ylpyrimidin-4-yl)-L-leucinamide,₁

N~1~-(Cyanomethyl)-N~2~-{2-(4-phenylpiperazin-1-yl)pyrimidin-4-yl}-L-leucinamide,₁

N~1~-(Cyanomethyl)-N~2~-{2-[2-(hydroxymethyl)piperidin-1-yl]pyrimidin-4-yl}-L-leucinamide,₁

N~1~-(Cyanomethyl)-N~2~-{2-[(2R)-2-(hydroxymethyl)pyrrolidin-1-yl]pyrimidin-4-yl}-L-leucinamide,₁

N~1~-(Cyanomethyl)-N~2~-{2-(4-hydroxypiperidin-1-yl)pyrimidin-4-yl}-L-leucinamide,₁

N~1~-(Cyanomethyl)-N~2~-{2-[4-(2-furoyl)piperazin-1-yl]pyrimidin-4-yl}-L-leucinamide,₁

N~2~-{2-[3-(Aminocarbonyl)piperidin-1-yl]pyrimidin-4-yl}-N~1~-(cyanomethyl)-L-leucinamide,₁

N~1~-(Cyanomethyl)-N~2~-{2-[methyl(2-pyridin-2-ylethyl)amino]pyrimidin-4-yl}-L-leucinamide,₁

N~2~-{2-(4-Benzylpiperidin-1-yl)pyrimidin-4-yl}-N~1~-(cyanomethyl)-L-leucinamide,₁

N~1~-(Cyanomethyl)-N~2~-{2-(4-pyridin-2-ylpiperazin-1-yl)pyrimidin-4-yl}-L-leucinamide,₁

N~1~-(Cyanomethyl)-N~2~-{2-(4-phenylpiperidin-1-yl)pyrimidin-4-yl}-L-leucinamide,₁

N~1~-(Cyanomethyl)-N~2~-{2-[4-(2-hydroxyethyl)piperidin-1-yl]pyrimidin-4-yl}-L-leucinamide,

N~2~-{2-[4-(3-Chlorophenyl)piperazin-1-yl]pyrimidin-4-yl}-N~1~-(cyanomethyl)-L-leucinamide,

N~1~-(Cyanomethyl)-N~2~-{2-(4-phenoxy-piperidin-1-yl)pyrimidin-4-yl}-L-leucinamide,

N~1~-(Cyanomethyl)-N~2~-{2-(3-phenylpyrrolidin-1-yl)pyrimidin-4-yl}-L-leucinamide,

N~1~-(Cyanomethyl)-N~2~-{2-{methyl[(3-methylisoxazol-5-yl)methyl]amino}pyrimidin-4-yl}-L-leucinamide,

and pharmaceutically acceptable salts thereof.

8. (Canceled)

9. (Currently amended) A pharmaceutical composition which comprises a compound of the formula (I) as defined in ~~any one of claims 1 to 7~~ claim 1 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable diluent or carrier.

10. (Currently amended) A method for producing inhibition of a cysteine protease in a mammal, such as man, in need of such treatment, which comprises administering to said mammal an effective amount of a compound of the present invention as defined in ~~any one of claims 1 to 7~~ claim 1 or a pharmaceutically acceptable salt thereof.

11. (Currently amended) A method for treating pain, such as neuropathic pain, in a mammal, such as man, in need of such treatment, which comprises administering to said mammal an effective amount of a compound as defined in ~~any one of claims 1 to 7~~ claim 1, or a pharmaceutically acceptable salt thereof.

12. (New) A pharmaceutical composition which comprises a compound according to claim 7 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable diluent or carrier.

13. (New) A method for producing inhibition of a cysteine protease in a mammal, such as man, in need of such treatment, which comprises administering to said mammal an effective amount of a compound according to claim 7 or a pharmaceutically acceptable salt thereof.

14. (New) A method for treating pain, such as neuropathic pain, in a mammal, such as man, in need of such treatment, which comprises administering to said mammal an effective amount of a compound according to claim 7, or a pharmaceutically acceptable salt thereof.

15. (New) A compound according to claim 2 in which R^3 is hydrogen.

16. (New) A compound according to claim 2 in which R^4 is hydrogen.

17. (New) A compound according to claim 2 in which R^5 is hydrogen or phenyl optionally substituted by C_{1-6} alkyl or C_{1-6} alkoxy.

18. (New) A compound according to claim 3 in which R^3 is hydrogen.

19. (New) A compound according to claim 3 in which R^4 is hydrogen.

20. (New) A compound according to claim 3 in which R^5 is hydrogen or phenyl optionally substituted by C_{1-6} alkyl or C_{1-6} alkoxy.